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Date: January 9, 2004

Kimberly J. Prior

(Print Name)

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1742

Synese Jolidon, et al.

Serial No.: 10/613,785

Filed: July 3, 2003

For: **3-PHENYL-PROPIONAMIDO, 3-PHENYL-ACRYLAMIDO AND 3-PHENYL-PROPYNAMIDO
DERIVATIVES**

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Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

<u>Country</u>	<u>Application No.</u>	<u>Filing Date</u>
Europe	02015583.4	July 15, 2002

Respectfully submitted,

Kimberly J. Prior

Kimberly J. Prior

Attorney for Applicant

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described on the following
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Les documents fixés à
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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02015583.4

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk



Anmeldung Nr:
Application no.: 02015583.4
Demande no:

Anmeldetag:
Date of filing: 15.07.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

F. HOFFMANN-LA ROCHE AG

4070 Basel
SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

3-Phenyl-propionamido, 3-phenyl-acrylamido and 3-phenyl-propynamido derivatives as
MAO-B inhibitors

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C09B/

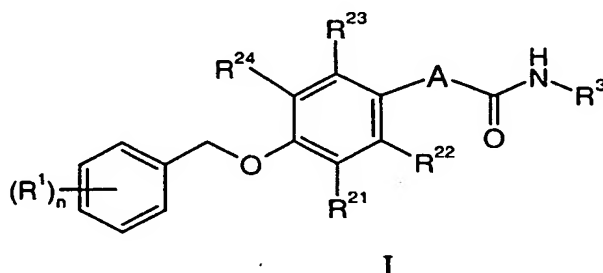
Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

Case 21288

3-Phenyl-propionamido, 3-phenyl-acrylamido and 3-phenyl-propynamido derivatives as
MAO-B inhibitors

This invention relates to 3-phenyl-propionamido, 3-phenyl-acrylamido or 3-phenyl-propynamido derivatives of the general formula



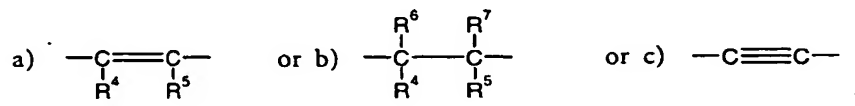
wherein

R^1 is C_1 - C_3 -alkyl, halogen, halogen- $(C_1$ - $C_6)$ -alkyl, cyano, C_1 - C_6 -alkoxy or halogen- $(C_1$ - $C_6)$ -alkoxy;

R^{21} , R^{22} , R^{23} and R^{24} independently from each other are selected from the group consisting of hydrogen and fluoro;

R^3 is hydrogen or C_1 - C_3 -alkyl;

A is



R^4 is hydrogen or C_1 - C_3 -alkyl;

R^5 is hydrogen or C_1 - C_6 -alkyl;

R^6 is hydrogen or C_1 - C_6 -alkyl;

R⁷ is hydrogen or C₁-C₆-alkyl; and
n is 1, 2 or 3.

The compounds of general formula I are selective monoamine oxidase B inhibitors.

Monoamine oxidase (MAO, EC 1.4.3.4) is a flavin-containing enzyme responsible
5 for the oxidative deamination of endogenous monoamine neurotransmitters such as
dopamine, serotonin, adrenaline, or noradrenaline, and trace amines, e.g. phenylethyl-
amine, as well as a number of amine xenobiotics. The enzyme exists in two forms, MAO-A
and MAO-B, encoded by different genes (A. W. Bach et al., *Proc. Natl. Acad. Sci. USA*
1988, 85, 4934-4938) and differing in tissue distribution, structure and substrate
10 specificity. MAO-A has higher affinity for serotonin, octopamine, adrenaline, and
noradrenaline; whereas the natural substrates for MAO-B are phenylethylamine and
tyramine. Dopamine is thought to be oxidised by both isoforms. MAO-B is widely
distributed in several organs including brain (A.M. Cesura and A. Pletscher, *Prog. Drug*
Research 1992, 38, 171-297). Brain MAO-B activity appears to increase with age. This
15 increase has been attributed to the gliosis associated with aging (C.J. Fowler et al., *J.*
Neural. Transm. 1980, 49, 1-20). Additionally, MAO-B activity is significantly higher in the
brains of patients with Alzheimer's disease (P. Dostert et al., *Biochem. Pharmacol.* 1989, 38,
555-561) and it has been found to be highly expressed in astrocytes around senile plaques
(Saura et al., *Neuroscience* 1994, 70, 755-774). In this context, since oxidative deamination
20 of primary monoamines by MAO produces NH₃, aldehydes and H₂O₂, agents with
established or potential toxicity, it is suggested that there is a rationale for the use of
selective MAO-B inhibitors for the treatment of dementia and Parkinson's disease.
Inhibition of MAO-B causes a reduction in the enzymatic inactivation of dopamine and
thus prolongation of the availability of the neurotransmitter in dopaminergic neurons.
25 The degeneration processes associated with age and Alzheimer's and Parkinson's diseases
may also be attributed to oxidative stress due to increased MAO activity and consequent
increased formation of H₂O₂ by MAO-B. Therefore, MAO-B inhibitors may act by both
reducing the formation of oxygen radicals and elevating the levels of monoamines in the
brain.

30 Given the implication of MAO-B in the neurological disorders mentioned above,
there is considerable interest to obtain potent and selective inhibitors that would permit
control over this enzymatic activity. The pharmacology of some known MAO-B inhibitors
is for example discussed by D. Bentué-Ferrer et al. in *CNS Drugs* 1996, 6, 217-236.
Whereas a major limitation of irreversible and non-selective MAO inhibitor activity is the
35 need to observe dietary precautions due to the risk of inducing a hypertensive crisis when
dietary tyramine is ingested, as well as the potential for interactions with other medications

(D. M. Gardner et al., *J. Clin. Psychiatry* 1996, 57, 99-104), these adverse events are of less concern with reversible and selective MAO inhibitors, in particular of MAO-B. Thus, there is a need for MAO-B inhibitors with a high selectivity and without the adverse side-effects typical of irreversible MAO inhibitors with low selectivity for the enzyme.

5 The object of the present invention therefore is to provide compounds which must have the advantageous properties mentioned above. It has been found that the compounds of formula I of the present invention show the potential to be highly selective MAO-B inhibitors. Subjects of the present invention are further a process for the manufacture of compounds of formula I as well as the use of the compounds of formula I in the control or
10 prevention of diseases mediated by monoamine oxidase B inhibitors, and, respectively, their use for the production of corresponding medicaments.

 The following definitions of general terms used in the present patent application apply irrespective of whether the terms in question appear alone or in combination. It must be noted that, as used in the specification and the appended claims, the singular
15 forms "a", "an," and "the" include plural forms unless the context clearly dictates otherwise.

 The term " C_1 - C_6 -alkyl" ("lower alkyl") used in the present application denotes straight-chain or branched saturated hydrocarbon residues with 1 to 6 carbon atoms, preferably with 1 to 3 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, and the like. Accordingly, the term " C_1 - C_3 -alkyl" means a straight-chain or
20 branched saturated hydrocarbon residue with 1 to 3 carbon atoms.

 The term "halogen" denotes fluorine, chlorine, bromine and iodine.

 "Halogen- $(C_1$ - $C_6)$ -alkyl" or "halogen- $(C_1$ - $C_6)$ -alkoxy" means the lower alkyl residue or lower alkoxy residue, respectively, as defined herein substituted in any position with one or more halogen atoms as defined herein. Examples of halogenalkyl residues include,
25 but are not limited to, 1,2-difluoropropyl, 1,2-dichloropropyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, and 1,1,1-trifluoropropyl, and the like. "Halogen-alkoxy" includes trifluoromethyloxy.

 " C_1 - C_6 -Alkoxy" means the residue -O-R, wherein R is a lower alkyl residue as defined herein. Examples of alkoxy radicals include, but are not limited to, methoxy, ethoxy,
30 isopropoxy, and the like.

 "Pharmaceutically acceptable salts" of a compound means salts that are pharmaceutically acceptable, which are generally safe, non-toxic, and neither biologically nor otherwise undesirable, and that possess the desired pharmacological activity of the parent compound. These salts are derived from an inorganic or organic acid or base. If

possible, compounds of formula I may be converted into pharmaceutically salts. It should be understood that pharmaceutically acceptable salts may be included in the present invention and that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) of the same acid addition salt.

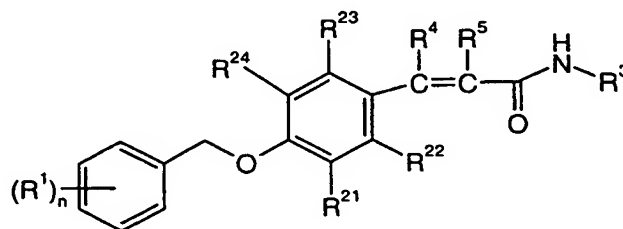
5 Among compounds of the present invention certain compounds of formula I are preferred.

Compounds of formula I are substituted by one, two or three R^1 selected from the group consisting of C_1 - C_3 -alkyl, halogen, halogen- $(C_1$ - $C_6)$ -alkyl, cyano, C_1 - C_6 -alkoxy or halogen- $(C_1$ - $C_6)$ -alkoxy, preferably they are substituted by one R^1 . Preferred compounds
10 of formula I are those, wherein R^1 is halogen or halogen- $(C_1$ - $C_6)$ -alkyl. Especially preferred are those compounds of formula I, wherein R^1 is fluoro or trifluoromethyl.

R^{21} , R^{22} , R^{23} and R^{24} independently from each other are selected from the group consisting of hydrogen or fluoro. Preferably, R^{21} , R^{22} , R^{23} and R^{24} are hydrogen.

R^3 is hydrogen or C_1 - C_3 -alkyl. Preferably, R^3 is hydrogen or methyl, and even more
15 preferably, R^3 is methyl.

Preferred are compounds of formula I, wherein A is $-CR^4=CR^5-$, i.e. compounds having the formula



I-a

Preferred are compounds of formula I-a wherein R^4 and R^5 independently from each
20 other are hydrogen or C_1 - C_3 -alkyl. All cis- and trans- isomers are included. Especially preferred are compounds of formula I-a, wherein A is $-CR^4=CR^5-$ and R^3 is methyl.

A preferred group of compounds within this group are those, wherein R^1 is $(C_1$ - $C_3)$ -alkyl or C_1 - C_6 -alkoxy.

Examples of such compounds are the following:

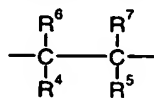
25 N-methyl-3-[4-(4-methyl-benzyloxy)-phenyl]-acrylamide and
3-[4-(3-methoxy-benzyloxy)-phenyl]-N-methyl-acrylamide.

Even more preferred are compounds of formula I-a, wherein R^4 and R^5 independently from each other are hydrogen or C_1 - C_3 -alkyl, R^3 is methyl and R^1 is fluoro or trifluoromethyl.

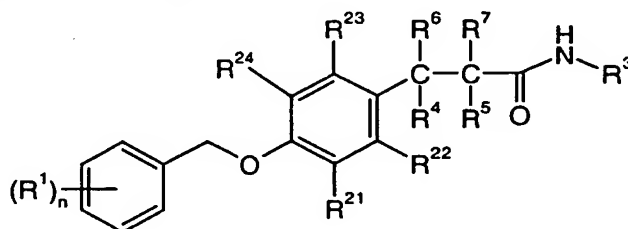
The following compounds are examples therefore:

- 3-[4-(3-fluoro-benzyloxy)-phenyl]-2,N-dimethyl-acrylamide,
- 3-[4-(3-fluoro-benzyloxy)-phenyl]-N-methyl-acrylamide,
- N-methyl-3-[4-(4-trifluoromethyl-benzyloxy)-phenyl]-acrylamide,
- 5 3-[4-(3,4-difluoro-benzyloxy)-phenyl]-N-methyl-acrylamide, and
- 3-[4-(4-fluoro-benzyloxy)-phenyl]-N-methyl-acrylamide.

Also preferred are compounds of formula I, wherein A is



and R⁴, R⁵, R⁶ and R⁷ independently from each other are hydrogen or C₁-C₃-alkyl, i.e. compounds having the formula

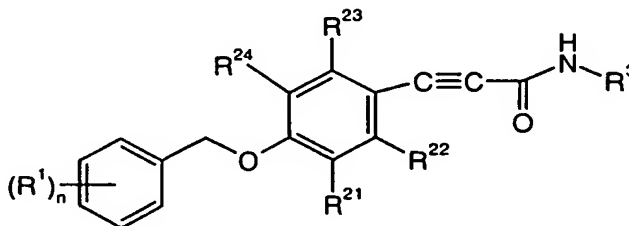


I-b

Examples of such compounds are the following:

- 3-[4-(3-fluoro-benzyloxy)-phenyl]-2,N-dimethyl-propionamide,
- 3-[4-(3,4-difluoro-benzyloxy)-phenyl]-propionamide, and
- 3-[4-(3-fluoro-benzyloxy)-phenyl]-N-methyl-butyramide.

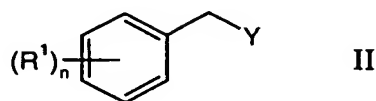
Further preferred are compounds of formula I, wherein A is -C≡C-, i.e. compounds of formula I having the formula



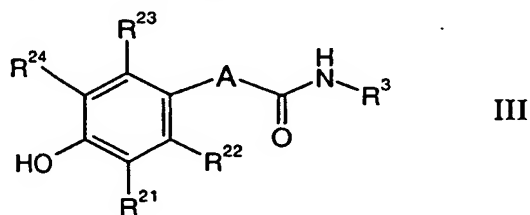
I-c

3-[4-(3-Fluoro-benzyloxy)-phenyl]-propynoic acid methylamide is an example for such a compound.

The compounds of general formula I can be manufactured by reacting a compound of formula

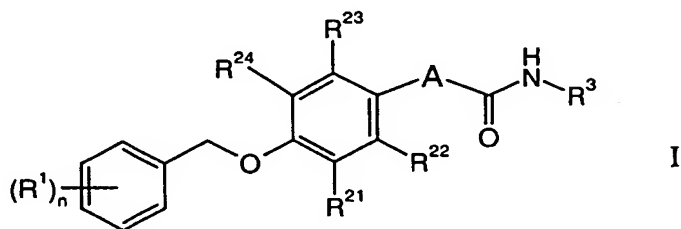


wherein Y is a leaving group, with a compound of formula



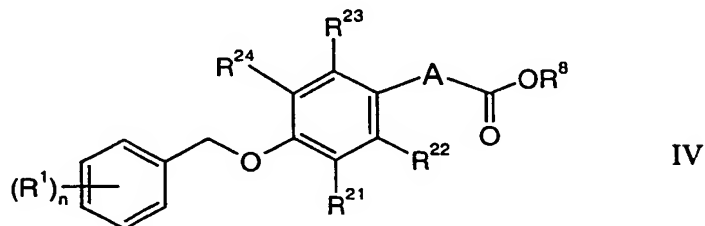
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to obtain a compound of formula



or, alternatively,

reacting a compound of formula

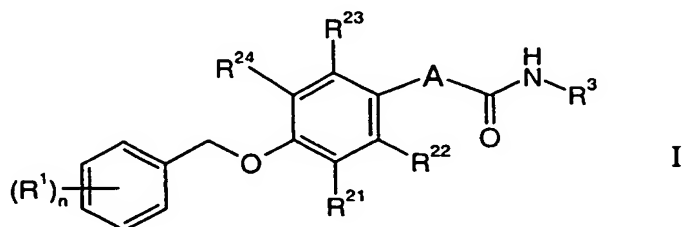


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wherein R⁸ is hydrogen or C₁-C₆-alkyl,
with an amine of formula



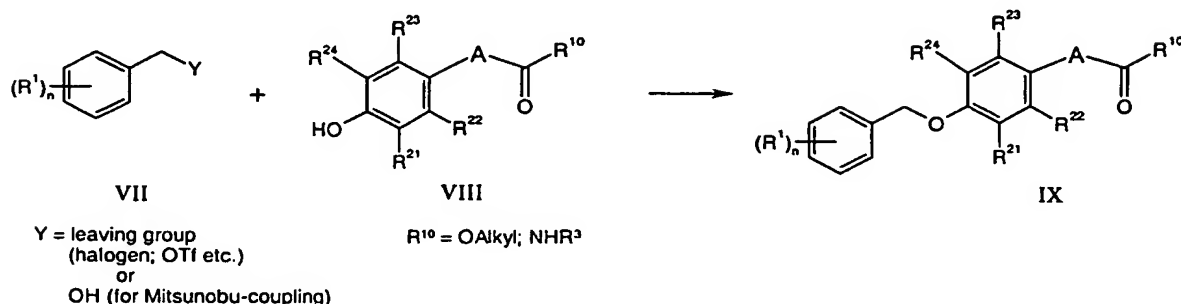
to obtain a compound of formula



15

In accordance with the present invention, a possibility to prepare compounds of general formula I is shown in scheme 1:

Scheme 1

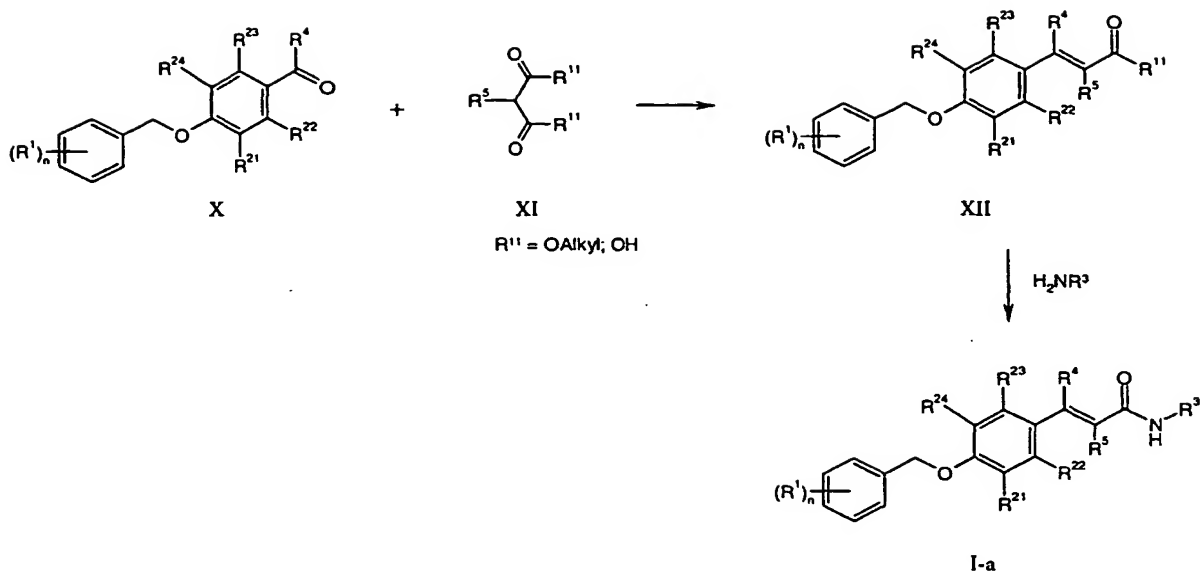


- 5 Compounds of the type IX are formed by Williamson-ether synthesis, starting from the corresponding p-substituted phenols VIII and benzylic halides, tosylates, mesylates or triflates VII. Bases used can be for example alcoholates or carbonates (sodium, potassium or cesium carbonate). Preferred solvents are lower alcohols, acetonitrile or lower ketones at temperatures between 20 °C and reflux temperature. Another approach is the
- 10 Mitsunobu-coupling of benzylic alcohols with the corresponding phenols VIII. The reaction is done as usual in inert solvents like for example diethyl ether or tetrahydrofuran, using dialkyl-azo-dicarboxylates in presence of phosphines (for example tributyl- or triphenyl-phosphine). When R^{10} is NHR^3 , these reactions lead directly to the desired compounds of formula I. If R^{10} is OAlkyl , the ester of formula IX can be transformed into
- 15 the desired final product of general formula I using standard procedures: aminolysis with R^3NH_2 in solvents like methanol, tetrahydrofuran etc., or saponification to the acid (for example KOH in methanol), activation of the acid via acid chloride (thionyl chloride or oxalyl chloride) or activation with N,N'-Dicyclohexylcarbodiimide (DCC), N-(3-dimethylamino-propyl)-N'-ethyl-carbodiimide hydrochloride (EDC) etc. and coupling
- 20 with the amine R^3NH_2 .

Another method (Scheme 2) to prepare compounds of formula I where A is $-\text{CR}^3=\text{CR}^4-$ involves Knoevenagel-Doebner condensations of the ketones or aldehydes X with malonate or dialkyl malonates. These reactions are done under standard conditions, using pyridine as a solvent, with or without piperidine catalysis, preferentially at reflux

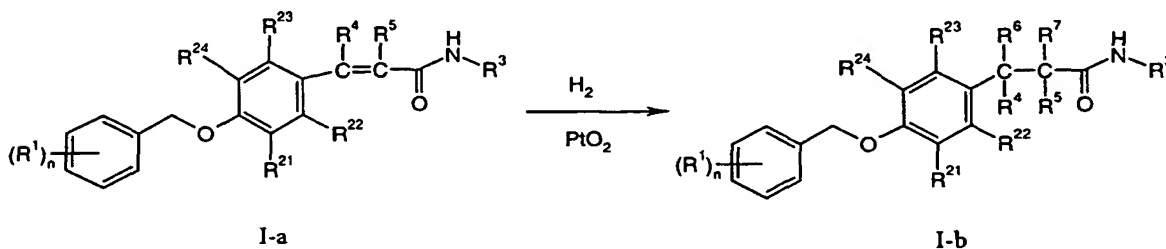
25 temperature.

Scheme 2



- The esters XII ($R^{11} = OAlkyl$) or acids XII ($R^{11} = OH$) are then converted as previously described to the desired amides of formula I-a. Alternatively, the compounds XII can be reduced to the derivatives I-b wherein $A = -CHR^4-CHR^5-$, previously to or following conversion to the amides (scheme 3). This reduction is preferentially done by catalytic hydrogenation using hydrogen and platinum on charcoal in solvents like methanol, dioxane or ethyl acetate at room temperature.

Scheme 3



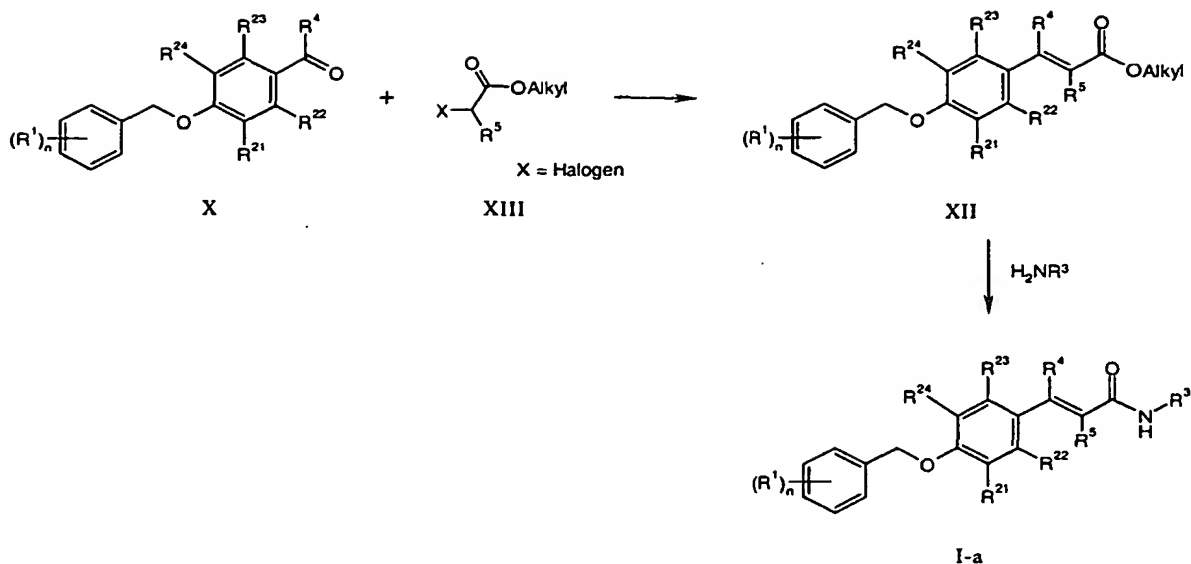
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The compounds X can be prepared by alkylation of optionally substituted 4-hydroxy-benzaldehydes or 4-hydroxy-acetophenones with benzylic halides, tosylates, mesylates or triflates in a reaction similar to the one depicted in scheme 1.

- Compounds of formula I wherein A is $-CR^3=CR^4-$ can also be prepared by a Reformatsky-reaction on compounds X (scheme 4).

15

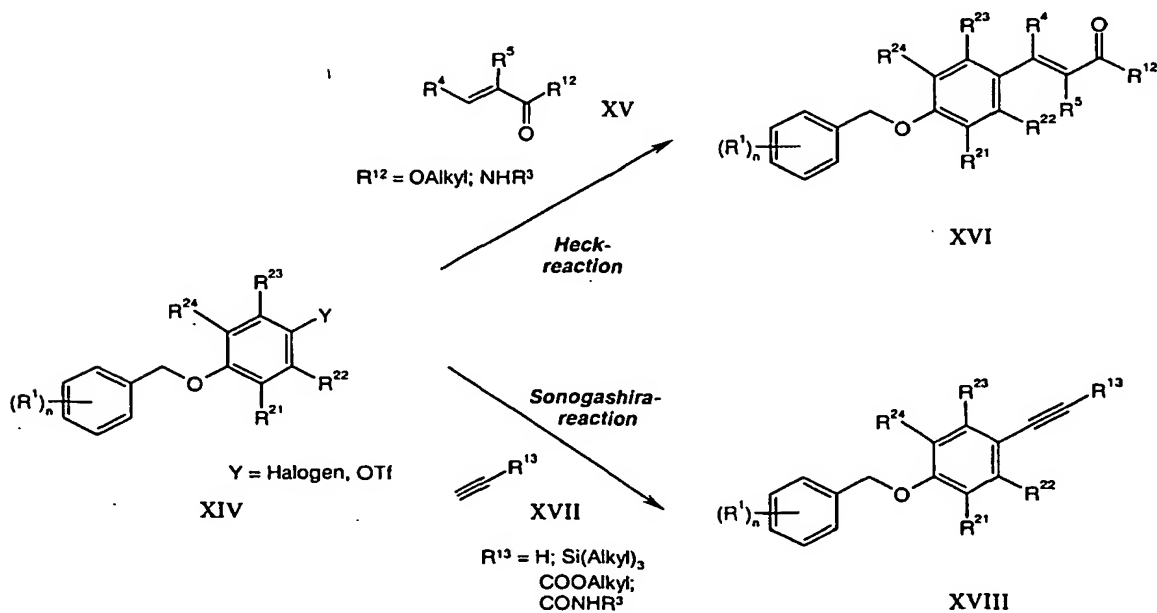
Scheme 4



These condensations of the carbonyl compounds with the alpha-halo-esters are done under standard conditions in ethers like diethyl ether, tetrahydrofuran or dioxane with preferentially zinc as a metal. Compounds XII can be further converted as previously described to the desired amides of formula I-a.

Another method (scheme 5) to prepare compounds of the type I-a or I-c involves Heck- or Sonogashira-couplings of aryl halides or triflates E with alkenes, respectively alkynes.

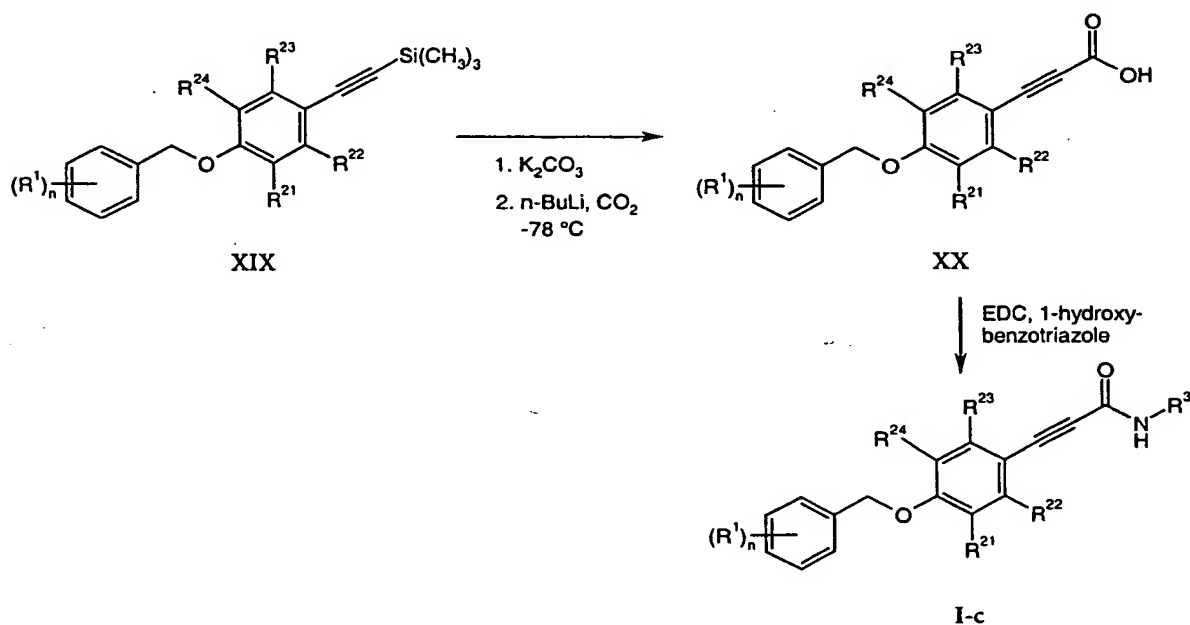
Scheme 5



Heck-reactions were performed using standard procedures (see P. D. Greenspan et al., *J. Med. Chem.* 1999, 42, 164 or M. Hanack et al., *Eur. J. Org. Chem.* 1999, 3441).

Sonogashira-couplings can be done using palladium catalysis under standard conditions (K.S.Y. Lau et al., *J. Org. Chem.* 1981, 46, 2280 or J. Ipaktschi et al., *Synth. Commun.* 1998, 28, 327).

Compounds of the type XVI, wherein R^{12} is OAlkyl, are converted to the amides I-a ($A = -CR^3=CR^4-$) by the procedures described earlier. Compounds of the type XVIII, wherein R^{13} is $-Si(Alkyl)_3$, are converted to the amides I-c ($A = -C\equiv C-$) by standard procedures, as described for example in scheme 6.



10

The compounds of formula I are, as already mentioned above, monoamine oxidase B inhibitors and can be used for the treatment or prevention of diseases in which MAO-B inhibitors might be beneficial. These include acute and chronic neurological disorders, cognitive disorders and memory deficits. Treatable neurological disorders are for instance traumatic or chronic degenerative processes of the nervous system, such as Alzheimer's disease, other types of dementia, minimal cognitive impairment or Parkinson's disease. Other indications include psychiatric diseases such as depression, anxiety, panic attack, social phobia, schizophrenia, eating and metabolic disorders such as obesity as well as the prevention and treatment of withdrawal syndromes induced by abuse of alcohol, nicotine and other addictive drugs. Other treatable indications may be reward deficiency syndrome (G.M. Sullivan, International patent application No. WO 01/34172 A2), peripheral neuropathy caused by cancer chemotherapy (G. Bobotas, International Patent Application

20

No. WO 97/33572 A1), or the treatment of multiple sclerosis (R.Y. Harris, International patent application No. WO 96/40095 A1) and other neuroinflammatory diseases.

The compounds of formula I are especially useful for the treatment and prevention of Alzheimer's disease and senile dementia.

- 5 The pharmacological activity of the compounds was tested using the following method:

 The cDNA's encoding human MAO-A and MAO-B were transiently transfected into EBNA cells using the procedure described by E.-J. Schlaeger and K. Christensen (Transient Gene Expression in Mammalian Cells Grown in Serum-free Suspension Culture; 10 Cytotechnology, 15: 1-13, 1998). After transfection, cells were homogenised by means of a Polytron homogenizer in 20 mM Tris HCl buffer, pH 8.0, containing 0.5 mM EGTA and 0.5 mM phenylmethanesulfonyl fluoride. Cell membranes were obtained by centrifugation at 45,000 x g and, after two rinsing step with 20 mM Tris HCl buffer, pH 8.0, containing 0.5 mM EGTA, membranes were eventually re-suspended in the above buffer and aliquots 15 stored at -80 °C until use.

 MAO-A and MAO-B enzymatic activity was assayed in 96-well-plates using a spectrophotometric assay adapted from the method described by M. Zhou and N. Panchuk-Voloshina (A One-Step Fluorometric Method for the Continuous Measurement of Monoamine Oxidase Activity, Analytical Biochemistry, 253: 169-174, 1997). Briefly, 20 membrane aliquots were incubated in 0.1 M potassium phosphate buffer, pH 7.4, for 30 min at 37 °C with or without various concentrations of the compounds. After this period, the enzymatic reaction was started by the addition of the MAO substrate tyramine together with 1 U/ml horse-radish peroxidase (Roche Biochemicals) and 80 µM N-acetyl-3,7,-dihydroxyphenoxazine (Amplex Red, Molecular Probes). The samples were further 25 incubated for 30 min at 37 °C in a final volume of 200 µl and absorbance was then determined at a wavelength of 570 nm using a SpectraMax plate reader (Molecular Devices). Background (non-specific) absorbance was determined in the presence of 10 µM clorgyline for MAO-A or 10 µM L-deprenyl for MAO-B.

 IC₅₀ values were determined from inhibition curves obtained using nine inhibitor 30 concentrations in duplicate, by fitting data to a four parameter logistic equation using a computer program.

 The compounds of the present invention are specific MAO-B inhibitors. The IC₅₀ values of preferred compounds of formula I as measured in the assay described above are in the range of 1 µM or less, typically 0.1 µM or less, and ideally 0.02 µM or less.

In the table below are described some specific IC₅₀ values of preferred compounds:

Compound	MAO-B IC ₅₀ (μmol)	MAO-A IC ₅₀ (μmol)
3-[4-(3-Fluoro-benzyloxy)-phenyl]-2-methyl-acrylamide	0.083	>10000
3-[4-(3-Fluoro-benzyloxy)-phenyl]-2,N-dimethyl-propionamide	0.029	>10000
3-[4-(3-Fluoro-benzyloxy)-phenyl]-propynoic acid amide	0.098	5620

The compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They may also contain other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

Example 1

3-[4-(3-Fluoro-benzyloxy)-phenyl]-2-methyl-acrylamide

a) 1-(3-Fluorobenzyloxy)-4-iodo-benzene

A solution of 3.0 g (15.9 mmol) of 4-iodophenol and 3.49 g (15.9 mmol) of 3-fluorobenzyl bromide in 30 ml ethanol is treated dropwise at room temperature with 20ml of a 1 molar solution of sodium ethanolate in ethanol. The reaction mixture is refluxed for 4 h and the precipitated sodium bromide is filtered off. The filtrate is evaporated to dryness, treated with 100 ml of water, acidified by addition of citric acid and extracted three times with dichloromethane. After drying and evaporation, the residue is subjected to chromatography on silica gel (hexane / ethyl acetate 9:1). This yields 4.23g (81 %) of a colorless solid. mp = 48 °C.

b) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-2-methyl-acrylic acid methyl ester

A mixture of 1.2 g (3.7 mmol) of 1-(3-fluorobenzyloxy)-4-iodo-benzene, 2.06 g (14.9mmol) of potassium carbonate and 1.70 g (52.8 mmol) of tetrabutyl ammonium bromide in 10 ml of dimethylformamide is treated under Ar with 48 mg (0.21 mmol) of palladium-(II)-acetate. 1.49 g (14.9 mmol) of methyl methacrylate is added and the mixture heated at 90 °C for about 40 min. The reaction mixture is poured into 150 ml dichloromethane, filtered and washed successively with 0.1 molar hydrochloric acid, saturated aqueous sodium hydrogencarbonate and water. The solution is dried over magnesium sulfate. Flash chromatography (silica gel, hexane / ethyl acetate 95:5) yields 461 mg (42%) of a colorless solid. MS: m/e = 301.3 (M⁺+H).

c) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-2-methyl-acrylic acid

383 mg (1.28 mmol) of 3-[4-(3-fluoro-benzyloxy)-phenyl]-2-methyl-acrylic acid methyl ester is added to a solution of 143 mg (2.55 mmol) potassium hydroxide in 7 ml methanol. The solution is stirred at 65 °C for about 3 h, evaporated to dryness, treated with aqueous 0.1 molar hydrochloric acid and extracted 3 times with ethyl acetate.

Evaporation of the solvent leaves the pure acid. 305 mg (84%) of a colorless solid. MS (neg.ions) : $m/e = 285.0$ (M-H).

d) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-2-methyl-acrylamide

305 mg (1.07 mmol) of 3-[4-(3-fluoro-benzyloxy)-phenyl]-2-methyl-acrylic acid is dissolved in 8 ml of dichloromethane and one drop of dimethylformamide is added. The solution is cooled to 0 °C and treated dropwise with 676 mg (5.33 mmol) oxalyl chloride. The resulting solution is stirred at 0 °C for additional 30 minutes, then 2 hours at room temperature. Evaporation of the solvent leaves the crude acid chloride which is dissolved in 5 ml tetrahydrofuran. This solution is slowly added under stirring to 10 ml of concentrated ammonia. The precipitate is filtered off and recrystallised from methanol to yield 199 mg (65%) of a colorless solid. MS: $m/e = 286.2$ ($M^+ + H$).

Example 2

3-[4-(3-Fluoro-benzyloxy)-phenyl]-2,N-dimethyl-acrylamide

The title compound is prepared in analogy to example 1 d), using aqueous methylamine instead of ammonia. Yield = 99%. Slightly yellow solid. MS: $m/e = 300.2$ ($M^+ + H$).

Example 3

3-[4-(3-Fluoro-benzyloxy)-phenyl]-2-methyl-propionamide

A solution of 50 mg of 3-[4-(3-fluoro-benzyloxy)-phenyl]-2-methyl-acrylamide in 10 ml methanol is treated with 4 mg of platinum dioxide and hydrogenated at room temperature and normal pressure for about 4 h. The catalyst is filtered off and the filtrate evaporated to dryness. Trituration of the residue in about 2 ml diethylether yields 12mg (23 %) of a colorless solid. MS: $m/e = 288.2$ ($M^+ + H$).

Example 4

3-[4-(3-Fluoro-benzyloxy)-phenyl]-2,N-dimethyl-propionamide

The title compound is prepared in analogy to example 3, starting from 3-[4-(3-fluoro-benzyloxy)-phenyl]-2,N-dimethyl-acrylamide. Yield = 52% of a colorless solid. MS: $m/e = 302.3$ ($M^+ + H$).

Example 5

3-[4-(3-Fluoro-benzyloxy)-phenyl]-propynoic acid amide

a) [4-(3-Fluoro-benzyloxy)-phenylethynyl]-trimethyl-silane

A well stirred suspension of 4.0 g (12.2 mmol) of 1-(3-fluorobenzyloxy)-4-iodo-
5 benzene, 0.23 g (1.22 mmol) of cuprous iodide and 0.856 mg (1.22 mmol) of dichloro
bis(triphenylphosphine) palladium(II) in a mixture of 20 ml tetrahydrofuran and 10 ml
triethylamine is treated dropwise with 1.44 g (14.6 mmol) of trimethylsilyl acetylene. The
reaction is exothermic. The mixture is stirred overnight at room temperature, treated with
saturated aqueous ammonium chloride and extracted three times with ethyl acetate. The
10 organic phase is dried, concentrated and subjected to flash-chromatography (silica gel,
cyclohexane) to yield 3.48 g (95%) of a slightly orange oil. NMR (CDCl₃; 300MHz) : 0.24
ppm (s, 9H); 5.06 ppm (s, 2H); 6.85-7.45 ppm (m, 8H).

b) 1-(3-Fluoro-benzyloxy)-4-ethynyl-benzene

A solution of 2.06 g (6.9 mmol) of [4-(3-fluoro-benzyloxy)-phenylethynyl]-
15 trimethyl-silane in 35 ml methanol is treated with 95 mg (0.69 mmol) of solid potassium
carbonate. The mixture is stirred at room temperature for 3 h, concentrated and treated
with saturated aqueous sodium hydrogencarbonate. The compound is extracted three
times with dichloromethane, dried over magnesium sulfate and concentrated to yield 1.53g
(98%) of a slightly brown oil. MS (neg.ions) : m/e = 225.4 (M-H).

20 c) [4-(3-Fluoro-benzyloxy)-phenyl]-propynoic acid

1.93 g (8.5 mmol) of 1-(3-fluoro-benzyloxy)-4-ethynyl-benzene is dissolved in 30 ml
tetrahydrofuran and cooled to -78 °C. 5.8ml (9.4mmol) of a 1.6 molar solution of n-butyl
lithium is slowly added under stirring. The resulting solution is stirred at -78 °C for 30
minutes. An excess of solid carbon dioxide is added and the suspension is slowly allowed
25 to warm to room temperature. Water is added and the mixture is acidified by addition of
aqueous 0.1 molar hydrochloric acid. Extraction with ethyl acetate yields a semi-solid
residue which is triturated in diethyl ether to give 1.58 g (68%) of a colorless solid. MS
(neg.ions) : m/e = 269.1 (M-H).

d) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-propynoic acid amide

30 50 mg (0.19 mmol) of [4-(3-fluoro-benzyloxy)-phenyl]-propynoic acid is dissolved
in 3ml of tetrahydrofuran and treated with 27 mg (0.2 mmol) of 1-hydroxybenzotriazole
and 37 mg (0.19 mmol) of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide
hydrochloride. The resulting mixture is stirred at room temperature for 30 minutes,

cooled to 0 °C and treated with 1 ml of concentrated ammonia. The suspension is stirred overnight at room temperature, diluted with water and extracted three times with dichloromethane. Flash-chromatography (silica gel, dichloromethane / methanol) yields 29 mg (59%) of a colorless solid. MS: $m/e = 270.2$ ($M^+ + H$).

5

Example 6

3-[4-(3-Fluoro-benzyloxy)-phenyl]-propynoic acid methylamide

The title compound is prepared in analogy to example 5 d), starting from [4-(3-fluoro-benzyloxy)-phenyl]-propynoic acid and aqueous methylamine. Colorless solid. Yield = 45%. MS: $m/e = 284.1$ ($M^+ + H$).

10

Example 7

3-[4-(3,4-Difluoro-benzyloxy)-phenyl]-propionamide

A mixture of 106 mg (0.64 mmol) 3-(4-Hydroxy-phenyl)-propionamide, 178 mg (1.29 mmol) potassium carbonate and 140 mg (0.68 mmol) 3,4-difluorobenzyl bromide in 5 ml ethyl methyl ketone is held at 50 °C for 24 hours. The reaction mixture is cooled, diluted with water and extracted with diethyl ether. Crystallization from n-hexane yields 77 mg (41 %) of a colorless solid. MS: $m/e = 291.3$ (M^+).

15

Example 8

3-[4-(3-Fluoro-benzyloxy)-phenyl]-N-methyl-acrylamide

a) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-acrylic acid 3-fluoro-benzyl ester

20

A mixture of 5.0 g (30.5 mmol) p-cumaric acid, 8.4 g (61 mmol) potassium carbonate and 11.5 g (61 mmol) 3-fluorobenzylbromide in 500 ml ethyl methyl ketone is held over night at 80 °C. The reaction mixture is cooled, diluted with water and extracted with ethyl acetate. Chromatography (silica gel, n-hexane / ethyl acetate 4:1) gives 6.48 g (56 %) of a colorless solid. MS: $m/e = 380.2$ (M^+).

25

b) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-acrylic acid

6.48 g (17 mmol) 3-[4-(3-fluoro-benzyloxy)-phenyl]-acrylic acid 3-fluoro-benzyl ester is dissolved in 100 ml tetrahydrofuran and 1.36 g (34 mmol) solid sodium hydroxide is added. The reaction mixture is heated overnight at 50 °C, cooled and acidified with 1N hydrochloric acid. The precipitate is filtered off and washed with cold water to give 4.43 g (96 %) of a colorless solid. MS: $m/e = 271.2$ ($M - H$).

30

c) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-acryloyl chloride

3.0 g (11 mmol) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-acrylic acid is suspended in 50 ml dichloromethane and 4.0 ml (55 mmol) of thionyl chloride is added. The reaction mixture is hold at room temperature for 1 hour, then heated to 50 °C overnight.

- 5 Evaporation yields 3.56 g (111 %) of the crude acid chloride as a yellowish solid. MS: $m/e = 290.2 (M^+)$.

d) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-N-methyl-acrylamide

- 500 mg (1.72 mmol) of the crude 3-[4-(3-fluoro-benzyloxy)-phenyl]-acryloyl chloride is dissolved in 2 ml dichloromethane and 0.4 ml of a 41 % solution of
10 methylamine in water is added. The reaction mixture is heated under reflux for about 3 hours, cooled, filtered and washed with cold dichloromethane to yield 149 mg (30%) of a colorless solid. MS: $m/e = 286.2 (M^+)$.

Example 9

3-[4-(3-Fluoro-benzyloxy)-phenyl]-acrylamide

- 15 500 mg (1.72 mmol) of the crude 3-[4-(3-Fluoro-benzyloxy)-phenyl]-acryloyl chloride as prepared in Example 8c) is dissolved in 2 ml dichloromethane and 4 ml of concentrated ammonia is added. The mixture is hold at reflux temperature for about 4 hours, cooled and filtered. The solid is subjected to column chromatography (silica gel, dichloromethane / methanol / ammonia 140 : 10 : 1) to give 89 mg (19 %) of a colorless
20 solid. MS: $m/e = 272.2 (M^+ + H)$.

Example 10

N-Ethyl-3-[4-(3-fluoro-benzyloxy)-phenyl]-acrylamide

- The title compound is prepared in analogy to example 9, using crude 3-[4-(3-Fluoro-benzyloxy)-phenyl]-acryloyl chloride and a 2 M solution of ethylamine in
25 dichloromethane. Colorless solid. Yield = 72 %. MS: $m/e = 300.3 (M^+ + H)$.

Example 11

N-Methyl-3-[4-(4-trifluoromethyl-benzyloxy)-phenyl]-acrylamide

a) 3-(4-Hydroxy-phenyl)-N-methyl-acrylamide

- 6.0 g (36.5 mmol) p-cumaric acid is dissolved in 10 ml dichloromethane. 3 drops of
30 N,N-dimethylformamide is added, followed by 10 ml of thionyl chloride. The mixture is

stirred at room temperature for 15 min, concentrated and treated with 5 ml of a 41 % solution of methylamine in water. After stirring at room temperature for about 2 hours, the methylamine is stripped off and the residue treated with water, extracted with dichloromethane and subjected to column chromatography (silica gel, dichloromethane / methanol / ammonia 140 : 10 : 1), yielding 670 mg (10 %) of a colorless solid. MS: $m/e = 177$ (M^+).

b) N-Methyl-3-[4-(4-trifluoromethyl-benzyloxy)-phenyl]-acrylamide

195 mg (1.1 mmol) 3-(4-hydroxy-phenyl)-N-methyl-acrylamide is dissolved in 25 ml ethyl methyl ketone and 304 mg (2.2 mmol) potassium carbonate is added, followed by 289 mg (1.2 mmol) of 4-(trifluoromethyl)benzyl bromide. The reaction mixture is stirred overnight at room temperature, heated to 50 °C for 3 hours, treated with water and extracted 3 times with dichloromethane. The extract is dried over magnesium sulfate, concentrated and treated with ether to yield 260 mg (70 %) of a colorless solid. MS: $m/e = 336.1$ ($M^+ + H$).

Example 12

3-[4-(3,4-Difluoro-benzyloxy)-phenyl]-N-methyl-acrylamide

a) 3-[4-(3,4-Difluoro-benzyloxy)-phenyl]-acrylic acid

2.5 g (15.2 mmol) p-cumaric acid is dissolved in 100 ml ethyl methyl ketone: 4.21 g (30.5 mmol) potassium carbonate and 6.31 g (30.5 mmol) 3,4-difluorobenzyl bromide is added and the reaction mixture held at 70 °C over night. Dilution with water and extraction with ethyl acetate leaves a solid which is recrystallised from diethyl ether / n-hexane. The crude ester so obtained is dissolved in 100 ml tetrahydrofuran and treated with 30.5 ml (30.5 mmol) of an aqueous 1 N sodium hydroxide solution. The mixture is heated to 50 °C for 6 hours, cooled and acidified with 1 N hydrochloric acid. The precipitate is filtered off and dried to yield 3.24 g (73 %) of a colorless solid. MS: $m/e = 288.9$ ($M-H$).

b) 3-[4-(3,4-Difluoro-benzyloxy)-phenyl]-N-methyl-acrylamide

500 mg (1.72 mmol) 3-[4-(3,4-difluoro-benzyloxy)-phenyl]-acrylic acid is suspended in 5 ml dichloromethane. 0.62 ml (8.6 mmol) thionyl chloride is added and the reaction mixture heated overnight to 45 °C. Concentration leaves a yellowish tar which is dissolved again in 10 ml dichloromethane and treated with 1.1 ml of a 33 % solution of methylamine in ethanol. After heating at 45 °C for 3 hours, the reaction mixture is filtered

and the filtrate concentrated. Chromatography (silica gel, dichloromethane / methanol) yields 136 mg (26 %) of a colorless solid. MS: $m/e = 304.1$ ($M^+ + H$).

Example 13

3-[4-(4-Fluoro-benzyloxy)-phenyl]-N-methyl-acrylamide

5 a) 3-[4-(4-Fluoro-benzyloxy)-phenyl]-acrylic acid

The title compound is prepared in analogy to example 12 a) from p-cumaric acid and 4-fluorobenzyl bromide. Yield = 56 %. Colorless solid. MS: $m/e = 271.0$ ($M - H$).

b) 3-[4-(4-Fluoro-benzyloxy)-phenyl]-N-methyl-acrylamide

10 The title compound is prepared in analogy to example 12 b) from 3-[4-(4-Fluoro-benzyloxy)-phenyl]-acrylic acid and methylamine. Yield = 21 %. Colorless solid. MS: $m/e = 286.0$ ($M^+ + H$).

Example 14

3-[4-(3-Cyano-benzyloxy)-phenyl]-N-methyl-acrylamide

15 The title compound is prepared in analogy to example 11 b) from 3-(4-hydroxy-phenyl)-N-methyl-acrylamide and 3-bromomethyl-benzonitrile. Yield = 75 %. Colorless solid. MS: $m/e = 293.2$ ($M^+ + H$).

Example 15

N-Methyl-3-[4-(4-methyl-benzyloxy)-phenyl]-acrylamide

20 The title compound is prepared in analogy to example 11 b) from 3-(4-Hydroxy-phenyl)-N-methyl-acrylamide and 1-Bromomethyl-4-methyl-benzene. Yield = 44 %. Colorless solid. MS: $m/e = 282.0$ ($M^+ + H$).

Example 16

3-[4-(3-Methoxy-benzyloxy)-phenyl]-N-methyl-acrylamide

25 The title compound is prepared in analogy to example 11 b) from 3-(4-Hydroxy-phenyl)-N-methyl-acrylamide and 1-Bromomethyl-3-methoxy-benzene. Yield = 60 %. Colorless solid. MS: $m/e = 298.2$ ($M^+ + H$).

Example 17

3-[4-(3-Fluoro-benzyloxy)-phenyl]-but-2-enoic acid methylamide

a) 1-[4-(3-Fluoro-benzyloxy)-phenyl]-ethanone

A mixture of 7.5 g (55.1 mmol) 4-hydroxy-acetophenone, 10.93 g (57.8 mmol) 3-fluoro-benzylbromide and 19.74 g (60.6 mmol) cesium carbonate in 75 ml acetonitrile is stirred for 1 hour at room temperature, then hold 3 hours at reflux temperature. The reaction mixture is concentrated and treated with about 200 ml of ice-water. Extraction with ethyl acetate yields 12.82 g (95 %) of a slightly yellowish solid. MS: $m/e = 245.3$ ($M^+ + H$).

b) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-but-2-enoic acid methyl ester

6.72 g (40 mmol) of trimethylphosphonoacetate is added to 40 ml of a 1M solution of sodium methanolate in methanol. The mixture is stirred for 15 minutes at room temperature. A solution of 4.89 g (20 mmol) of 1-[4-(3-Fluoro-benzyloxy)-phenyl]-ethanone in 40 ml methanol is slowly added at room temperature. The resulting mixture is refluxed for 20 hours and concentrated, leaving 4.98 g of a yellowish solid. Chromatography on silica gel (cyclohexane / ethyl acetate 9:1) gives 1.169 g (19%) of yellowish oil which crystallises on standing. MS: $m/e = 301.3$ ($M^+ + H$).

c) 3-[4-(3-Fluoro-benzyloxy)-phenyl]-but-2-enoic acid methylamide

0.224 g (4 mmol) of KOH is dissolved in 10 ml methanol. 0.4 g (1.33 mmol) of 3-[4-(3-fluoro-benzyloxy)-phenyl]-but-2-enoic acid methyl ester is added and the resulting solution refluxed for 6 hours, concentrated and acidified with 2N aqueous hydrochloric acid. Extraction with ethyl acetate gives 325 mg (85%) of the crude acid. This acid is dissolved in 10 ml of dichloromethane, 2 drops of N,N-dimethylformamide are added and the mixture is cooled to 0 °C. Slow addition of 0.380 g (3mmol) of oxalylchloride yields a yellow solution which is stirred for additional 1.5 hours at room temperature. Evaporation of the reaction mixture leaves a yellowish resin which is dissolved in 5ml tetrahydrofurane and slowly added at 0 °C to a mixture of 5 ml tetrahydrofurane and 5 ml aqueous methylamine (40 %). The resulting slurry is stirred at room temperature for 1 hour, evaporated, diluted with water and extracted three times with ethyl acetate. Chromatography on silica gel (cyclohexane / ethyl acetate 1:1) gives 220 mg (50%) of a colorless solid. MS: $m/e = 300.2$ ($M^+ + H$).

Example 18

3-[4-(3-Fluoro-benzyloxy)-phenyl]-N-methyl-butyramide

- 100 mg (0.33mmol) of 3-[4-(3-Fluoro-benzyloxy)-phenyl]-but-2-enoic acid
methanamide is dissolved in 7 ml methanol. 25 mg of platinum 5 % on charcoal is added
5 and the mixture is hydrogenated at room temperature and normal pressure. The catalyst is
filtered off and the filtrate evaporated to dryness, leaving 81 mg of a colorless solid.
MS: $m/e = 302.3$ ($M^+ + H$).

Example A

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>
Active ingredient	100
5 Powdered lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
10 Tablet weight	<u>250</u>

Example B

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>
Active ingredient	200
15 Powdered lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
20 Tablet weight	<u>400</u>

Example C

Capsules of the following composition are produced:

	<u>mg/Capsule</u>
Active ingredient	50
5 Crystalline lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	<u>150</u>

- 10 The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

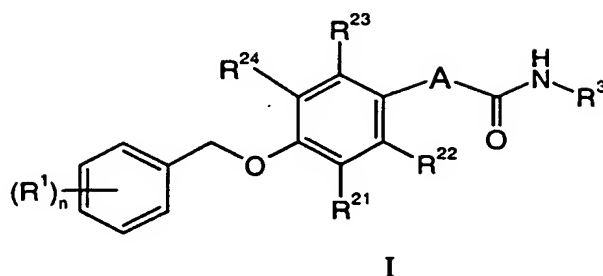
Example D

- 15 An injection solution may have the following composition and is manufactured in usual manner:

Active substance	1.0 mg
1 N HCl	20.0 µl
acetic acid	0.5 mg
20 NaCl	8.0 mg
phenol	10.0 mg
1 N NaOH	q.s. ad pH 5
H ₂ O	q.s. ad 1 ml

Claims

1. Compounds of the general formula



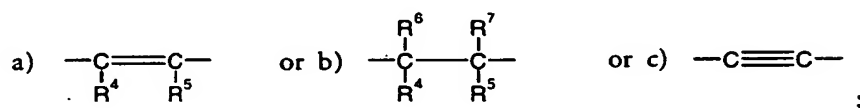
wherein

- 5 R^1 is C_1 - C_3 -alkyl, halogen, halogen- $(C_1$ - $C_6)$ -alkyl, cyano, C_1 - C_6 -alkoxy or halogen- $(C_1$ - $C_6)$ -alkoxy;

R^{21} , R^{22} , R^{23} and R^{24} independently from each other are selected from the group consisting of hydrogen and fluoro;

R^3 is hydrogen or C_1 - C_3 -alkyl;

- 10 A is



R^4 is hydrogen or C_1 - C_3 -alkyl;

R^5 is hydrogen or C_1 - C_6 -alkyl;

R^6 is hydrogen or C_1 - C_6 -alkyl;

- 15 R^7 is hydrogen or C_1 - C_6 -alkyl; and

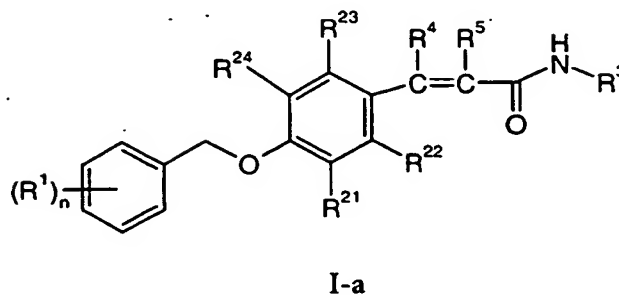
n is 1, 2 or 3.

2. Compounds of formula I according to claim 1, wherein R^1 is halogen or halogen- $(C_1$ - $C_6)$ -alkyl.

3. Compounds of formula I according to claim 1, wherein R^{21} , R^{22} , R^{23} and R^{24} are
20 hydrogen.

4. Compounds of formula I according to claim 1, wherein R^3 is methyl.

5. Compounds of formula I according to claim 1 having the formula



wherein R^1 , R^{21} , R^{22} , R^{23} , R^{24} , R^3 , R^4 and R^5 have the significances as defined in claim 1.

6. Compounds of formula I-A according to claim 5, wherein R^3 is methyl.

5 7. Compounds of formula I-A according to claim 6, wherein R^1 is C_1 - C_3 -alkyl or C_1 - C_6 -alkoxy.

8. Compounds of formula I-A according to claim 7, which compounds are selected from the group consisting of
N-methyl-3-[4-(4-methyl-benzyloxy)-phenyl]-acrylamide, and

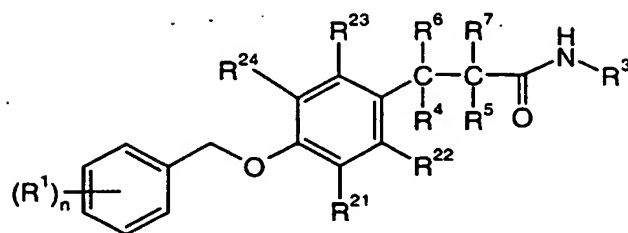
10 3-[4-(3-methoxy-benzyloxy)-phenyl]-N-methyl-acrylamide.

9. Compounds of formula I-A according to claim 6, wherein R^1 is fluoro or trifluoromethyl.

10. Compounds of formula I-A according to claim 8, which compounds are selected from the group consisting of

15 3-[4-(3-fluoro-benzyloxy)-phenyl]-2,N-dimethyl-acrylamide,
3-[4-(3-fluoro-benzyloxy)-phenyl]-N-methyl-acrylamide,
N-methyl-3-[4-(4-trifluoromethyl-benzyloxy)-phenyl]-acrylamide,
3-[4-(3,4-difluoro-benzyloxy)-phenyl]-N-methyl-acrylamide, and
3-[4-(4-fluoro-benzyloxy)-phenyl]-N-methyl-acrylamide.

11. Compounds of formula I according to claim 1 having the formula



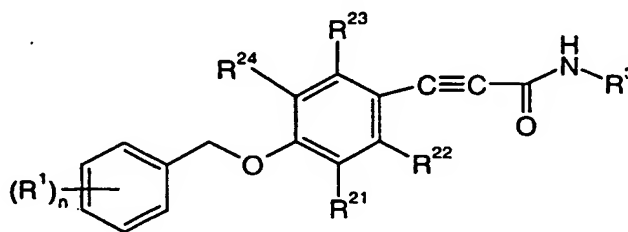
I-b

wherein R^1 , R^{21} , R^{22} , R^{23} , R^{24} , R^3 , R^4 , R^5 , R^6 and R^7 have the significances as defined in claim 1.

12. Compounds of formula I-B according to claim 11, which compounds are selected from the group consisting of

3-[4-(3-fluoro-benzyloxy)-phenyl]-2,N-dimethyl-propionamide,
3-[4-(3,4-difluoro-benzyloxy)-phenyl]-propionamide, and
3-[4-(3-fluoro-benzyloxy)-phenyl]-N-methyl-butylamide.

13. Compounds of formula I according to claim 1 having the formula



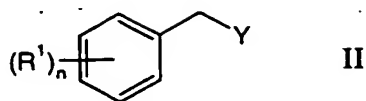
I-c

wherein R^1 , R^{21} , R^{22} , R^{23} , R^{24} and R^3 have the significances as defined in claim 1.

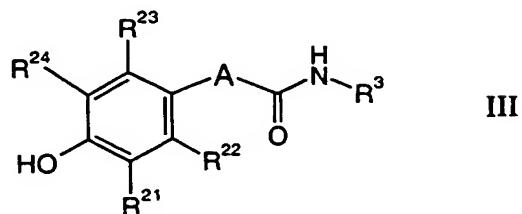
14. A compound of formula I-C according to claim 13, which is
3-[4-(3-fluoro-benzyloxy)-phenyl]-propynoic acid methylamide.

15. A process for the manufacture of a compound of formula I according to any one of claims 1 to 14, which process comprises

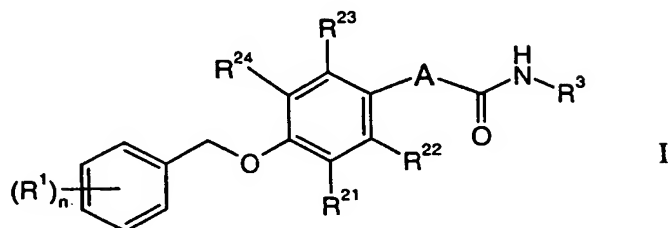
a) reacting a compound of formula



wherein Y is a leaving group, with a compound of formula

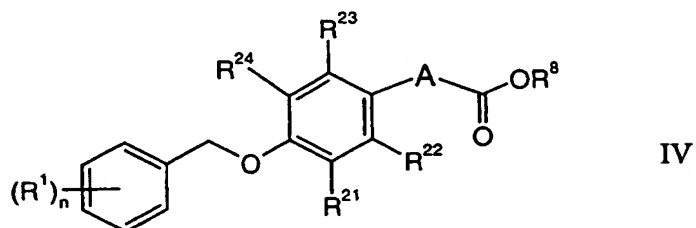


5 to obtain a compound of formula



or

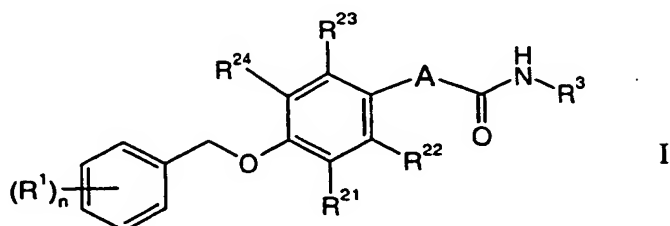
b) reacting a compound of formula



10 wherein R⁸ is hydrogen or C₁-C₆-alkyl,
with an amine of formula



to obtain a compound of formula



16. A compound of formula I according to any one of claims 1 to 14, when manufactured by a process according to claim 15.

17. A medicament containing one or more compounds as claimed in any one of claims 1 to 14 and pharmaceutically acceptable excipients for the treatment and
5 prevention of diseases which are mediated by monoamine oxidase B inhibitors.

18. The medicament according to claim 17 for the treatment and prevention of Alzheimer's disease and senile dementia.

19. A compound of formula I according to any one of claims 1 to 14 as well as its pharmaceutically acceptable salts for the treatment or prevention of diseases.

10 20. The use of a compound of formula I according to any one of claims 1 to 14 as well as its pharmaceutically acceptable salts for the manufacture of medicaments for the treatment and prevention of diseases which are mediated by monoamine oxidase B inhibitors.

15 21. The use according to claim 20, wherein the disease is Alzheimer's disease or senile dementia.

22. The invention as herein before described.
